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REVIEW ARTICLE

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The vaso-occlusive pain crisis: pathophysiology, and management

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Abstract

Early diagnosis, treatment, and prevention of a vaso-occlusive crisis (VOC) are critical to the management of patients with sickle cell disease. It is essential to differentiate between VOC-associated pain and chronic pain, hyperalgesia, neuropathy, and neuropathic pain. The pathophysiology of VOCs includes polymerization of abnormal sickle hemoglobin, inflammation, and adhesion. Hydroxyurea, L-glutamine, crizanlizumab, and voxelotor have been approved by the US Food and Drug Administration for reducing the frequency of VOCs; the European Medicines Agency has approved only hydroxyurea. Other novel treatments are in late-stage clinical development in both the United States and the European Union. The development of agents for prevention and treatment of VOCs should be driven by our understanding of its pathophysiology.

KEYWORDS
hydroxyurea, L-glutamine, pain, P-selectin, sickle cell disease

1 | INTRODUCTION

Sickle cell disease (SCD) is the most common hemoglobinopathy, with approximately 300 000 new cases each year and millions of patients affected globally.[1] In the United States, there are more than 230 000 hospital admissions related to SCD annually at an economic cost of $2.4 billion.[2] Acute episodes of pain, also commonly referred to as sickle cell pain crises, or vaso-occlusive crises (VOCs), are not only the primary presenting morbidity associated with SCD, but also the cause of hospitalization in approximately 95% of cases.[3] Furthermore, the frequency of VOCs, along with acute chest syndrome (ACS), is the most common predictor of death in patients with SCD.[4] Recurrent episodes have a significant impact on quality of life,[5] such that the incidence of pain may have a greater impact on quality of life than cumulative organ damage.[6]

The pain associated with VOC is often described as sudden in onset, throbbing, and sharp.[5] Common sites of pain include the lower back, joints, and extremities. Vaso-occlusive crisis is often preceded by a prodromal phase of 1-2 days, with pain peaking on Day 3 and lasting until Day 6 or Day 7 before resolving.[5] The average hospital stay is approximately 9-11 days in adults.[5] In addition to the pain associated with VOC, there are a number of clinical consequences. Acute chest syndrome, hepatic and renal involvement, cerebrovascular accident, and multi-organ failure resulting in death can develop in association with VOCs.[7-9] Acute chest syndrome occurs in 10%–20% of hospitalized patients with SCD, usually manifesting 1-3 days after admission for a severe VOC, and can, in some cases, progress rapidly to acute respiratory failure and death.[10] Thus, identification, treatment, and prevention of VOCs could significantly impact the natural history of the disease. The objective of this review was to discuss the pathophysiology, diagnosis, and management of VOC, and to distinguish between VOC and other causes of pain in patients with SCD.

2 | MECHANISMS OF VOC

In order to accurately diagnose, predict, or prevent the onset of VOC and associated pain and other sequelae, it is necessary to

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understand the underlying mechanisms. Chronic vascular inflammation causes activation of endothelial and blood cells leading to release of macrophages, mast cells, and platelets, multicellular adhesion, and activation of nociceptors, resulting in vaso-occlusion and VOC.[11,12] Vaso-occlusion is a multifactorial process involving not only occlusion of small blood vessels by sickled red blood cells (RBCs) and adherent blood cells, but also large-vessel intimal hyperplasia, thrombosis, and bone marrow fat embolization,[13] leading to hypoxia, ischemia, and tissue damage and inflammation.[4,14-16] It is this combination of hypoxia/reperfusion injury, ischemic tissue damage, and inflammation that makes SCD pain unique.[4]

2.1 Polymerization

Polymerization of deoxygenated sickle hemoglobin leads to decreased deformability of RBCs and is responsible for the characteristic "sickle" shape of RBCs in patients with SCD. Sickled RBCs are rigid and do not easily flow through the microcirculation; they can obstruct the vasculature, resulting in pain episodes and end-organ injury. Recurrent polymerization can lead to multiple RBC and systemic abnormalities, including hemolytic anemia and downstream progressive organ dysfunctions.[17,18] Recent data suggest that the overall percentage of sickled cells increases 1-3 days prior to the clinical crisis during the evolution of a VOC, which is followed by a decrease in sickled cells as patients recover. Therefore, while overall RBC deformability decreases early in the VOC, it increases later as the percentage of rigid cells decreases.[17-19]

2.2 Adhesion

Acute VOCs are believed to occur because of adherence of sickled RBCs to the vascular endothelium, adherent leukocytes, and platelets in small blood vessels. This multicellular adhesion, rather than changes in RBC morphology per se, is now thought to be the trigger for VOC and has been shown in animal models to lead to initiation of VOC.[20] Accumulation of sickled RBCs and other adherent cells may contribute to vaso-occlusion in smaller vessels in the absence of an inflammatory trigger.[17] Interaction of a number of adhesion molecules has been implicated in SCD, including α4β1 integrin, CD36 expression on sickle cell vs normal erythrocytes, basal cell adhesion molecule/lutheran protein, and endothelial vascular cell adhesion molecule-1 (VCAM-1).[20,21]

P-selectin is another adhesion molecule that is implicated in inflammation, coagulation, and atherosclerosis, and appears to be particularly important in SCD.[21] P-selectin is expressed on the surface of both endothelial cells and platelets, and has a role in the adhesion, rolling, and capture of blood cells.[22-24] Activated platelets bind to neutrophils in a P-selectin–dependent manner to form aggregates, and increased expression of P-selectin on endothelial cells promotes leukocyte adhesion, together contributing to the development of VOC.[25] Possible triggers described for this process include inflammation, stress, increased viscosity, decreased flow, and hemolysis.[15]

Summary Questions

1. What is the new aspect of your work?

This work discusses and reviews several potential treatments for the management of patients with frequent vascular occlusive crises associated with sickle cell disease other than opioids and hydroxyurea. These new treatments either have been approved or are in development.

2. What is the central finding?

Our current understanding of a vaso-occlusive crisis in patients with sickle cell disease (SCD) is that it is a multifactorial process characterized by inflammation, adhesion, and multicellular aggregation of sickled red blood cells, endothelial cells, platelets, and other blood cells, resulting in vaso-occlusion and acute severe pain. Prevention of vaso-occlusion and/or reduction in frequency of pain crises, especially in those at higher risk, should be considered foremost, as opposed to management protocols that treat pain with opioid administration.

3. What is (or could be) the significance/relevance of your work?

While management protocols to abort or ameliorate vaso-occlusive crises by administration of opioids have been developed and are widely in use, opioid medication does not address the underlying disease processes and may lead to hyperalgesia, dependence, and tolerance. Prevention of pain associated with these crises is a preferred approach whenever possible. Studies have shown that supplementation with L-glutamine decreases endothelial cell adhesion, suggesting that it may be useful for the prevention of vaso-occlusive crises; this drug was approved by the US Food and Drug Administration (FDA) in 2017 to reduce the complications of SCD in adult and pediatric patients 5 years of age and older. In 2019, voxelotor was approved by the FDA to treat patients with SCD 12 years of age and older, and crizanlizumab was approved by the FDA to reduce the frequency of vaso-occlusive crises. Other drugs are in clinical development as well. Education of hematologists and others who work in the field of SCD about these new agents should lead to improved protocols for patients with SCD, with an expected outcome of a reduction in vaso-occlusive crises.

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2.β Inflammation

The inflammatory chemokine CXCL1, which acts as a neutrophil chemoattractant, has been identified as a critical mediator of VOC in humanized SCD mice,[26] and neutrophil activation accompanied by an acute inflammatory response has been associated with VOC in patients who experience subsequent ACS.[27] Together, sickled RBCs, activated endothelial cells, neutrophils, leukocytes, and monocytes create a pro-inflammatory and pro-aggregatory environment.[15,28] Ischemia-reperfusion injury secondary to microvascular occlusions promotes chronic inflammation through increased oxidant production and increased adhesion of leukocytes, which further contributes to vaso-occlusion and tissue damage.[29] Inflammatory mediators TGF-β and IL-17 have been shown to be significantly increased in patients with SCD at steady state compared with controls; TNF-α, IL-6, and IL-8 are also significantly elevated compared with controls in patients with SCD and VOCs.[30]

3 | DIFFERENTIAL DIAGNOSIS AND DISTINGUISHING FEATURES OF VOC

The pain associated with VOC is typically acute and severe, often requiring treatment with parenteral opioids.[3] However, it is important to distinguish VOC pain from other pain syndromes commonly seen in SCD. For instance, many patients with SCD suffer from chronic pain as a result of bone infarction, avascular necrosis of the femoral or humeral head, leg ulcers, and chronic osteomyelitis. Some patients also experience intractable chronic pain without evident pathology.[5,31]

Chronic pain in SCD has been defined as ongoing pain that is present on most days over 3-6 months in a single or multiple locations.[5,32] Chronic pain is usually treated with long-acting or controlled-release opioids and does not require hospitalization unless severe or associated with an acute crisis, or if it is associated with severe infection as may happen with leg ulcers.[5,33] Pediatric patients with SCD are more likely to be pain-free between VOCs compared with adult patients with SCD; with increasing age, mild or moderate pain between crises becomes more common, complicating diagnosis and management.[5] Although acute pain is usually thought to be a consequence of VOC, it is also possible that pain itself may trigger vasoconstriction, leading to full-scale VOC.[34] It is estimated that 47% of adult patients with SCD in the United States take short-acting opioids and 27% take both short- and long-acting opioids, although the median daily dose of opioids is relatively low at 6.1 mg oral morphine equivalents.[33] A fraction of patients also take non-steroidal anti-inflammatory drugs (NSAIDs).[34]

Neuropathic pain is usually regarded as chronic, is usually described as numb, tingling, lancinating, spontaneous, shooting, or paroxysmal in nature, and may be associated with a sensation of pins and needles, hyperalgesia, and allodynia.[5] This is in contrast to the pain associated with VOC, which is described as pounding, cutting, gnawing, or like a generalized toothache.[5] Neuropathic pain is quite common in patients with SCD, with 37% having evidence of neuropathic pain in one study.[35,36] It is therefore critical to differentiate between neuropathic pain and acute and chronic pain seen in these patients. Neuropathic pain has also been shown to correlate with older age.[35,36] It is important to note that neuropathy and neuropathic pain are not the same. Neuropathic pain is usually defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system.[37] This type of pain usually occurs in concert with VOC and resolves after the crisis ends.[38] Drugs typically used for neuropathic pain, including gabapentin, pregabalin, and amitriptyline, have not been systematically studied in patients with SCD, but preliminary studies and case reports have suggested that they may have some efficacy, including reducing the frequency of VOCs.[39-41] A number of patient-reported outcome (PRO) scales, including the McGill Pain Questionnaire and PAIN*Report*It®, have been used to diagnose neuropathic pain in SCD.[38] Neuropathy, such as peripheral neuropathy, also occurs in SCD, with mental nerve neuropathy most commonly associated with VOC.[5,35] Although neuropathy is not always associated with pain, it may occur as a result of tissue damage to vessels and nerves following VOC.

When diagnosing VOC, the most important step is to differentiate it from acute flares of chronic pain that are often of unknown origin, but could be related to orthopedic complications of SCD, including bone infarction and avascular necrosis.[5,31] Diagnosis of VOC in children is complicated by the fact that VOC affecting the bone is the most common acute clinical manifestation of SCD in this population.[42] Vaso-occlusive crisis may also be confused with the much less frequently occurring osteomyelitis, which can be an acute or chronic inflammatory process caused by infection with pyogenic organisms due to impaired immune function and functional asplenia, leading to infection of the bone. Osteomyelitis is characterized by localized pain, tenderness, and swelling affecting a single site and a limited range of motion, and/or prolonged fever and pain. While the number of days of fever and pain prior to admission, as well as increased C-reactive protein levels and erythrocyte sedimentation rates, is considered to be key differentiators by some, often it is difficult to differentiate the two conditions.[42,43]

Neuropathic pain and hyperalgesia can also be difficult to distinguish from VOC. While hyperalgesia is a signature of neuropathic pain, it can also occur due to prolonged opioid use.[5] Opioid-induced hyperalgesia differs from tolerance in that increasing the opioid dose to manage pain paradoxically increases pain sensitivity, results in higher pain scores, and is accompanied by allodynia.[44]

It may also be necessary to differentiate ACS from VOC manifested in the pulmonary system.[45] Both present with fever, shortness of breath, chest pain, and leukocytosis. A new infiltrate on chest X-ray is diagnostic of ACS, which may appear normal early in an ACS episode.[46] However, pain usually precedes onset of ACS, with ACS occurring about 3 days after the onset of VOC.[9]

4 | PREDICTION OF VOC

Various predictive factors should heighten vigilance in monitoring for VOC and may be an indication for more aggressive management.

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For example, higher levels of fetal hemoglobin (HbF), typically with pan-cellular distribution, may be protective against VOC and other pathological consequences of SCD due to its interfering with polymerization of sickle hemoglobin during the sickling process,[47,48] and are also inversely related to mortality; individuals with low HbF levels may therefore be at greater risk of VOC.[4] In addition, some patients have reported symptoms of numbness, paresthesia, or aches before onset of VOC. In one study, 58% of patients with SCD reported these symptoms 1-2 days before VOC, suggestive of a prodromal phase.[49]

4.1 Triggers of VOC

Many patient-related and environmental factors have been shown to be risk factors for VOC and may also lead to hyperalgesia (Table 1).[50,51] Patient factors include hypoxia, infection, fever, acidosis, dehydration, pregnancy, menstruation, and obstructive sleep apnea; pain itself can also precipitate painful crises. Anxiety, depression, alcohol consumption, and physical exhaustion can also trigger onset of VOC. In addition, comorbidities such as sarcoidosis, diabetes, cholecystitis, and herpes can lead to pain crises. It has been suggested that these triggers may actually cause pain crises due to a link between the autonomic nervous system (ANS) and VOC.[51] Perturbations in the ANS in response to these triggers may cause ANS-mediated vasoconstriction, tipping the balance from steady state toward VOC. A recent study using mathematical models of biophysical markers indicated that markers relating to increased blood pressure were involved in pain-induced vasoconstriction.[52] These markers may allow for characterization of disease severity and risk of VOC, based on the underlying physiology rather than genotype.

Environmental factors such as exposure to extremes of temperature and higher wind speed have also been identified as triggers for VOC.[50,51] In one study, colder temperatures and higher wind speed were associated with a higher incidence of VOC in children under age 18 years.[53] The average monthly pain score was also significantly higher in more humid months.

4.2 Biomarkers of VOC

Some blood parameters have been associated with severity of SCD. As already discussed, neutrophils have a key role in the pathogenesis of VOC.[28] Higher neutrophil counts have been shown to correlate with more severe disease, including earlier death, and increased incidence of silent brain infarcts, hemorrhagic stroke, and ACS.[27] Although platelet counts have not consistently been shown to be associated with the frequency or severity of VOCs, platelet hyperactivity has been found to be increased during VOC. Plasma levels of platelet factors 3 and 4 are increased in patients with SCD at steady state and are even higher during VOC.[54] Notably, patients with SCD are capable of making platelet factor 3 available for coagulation activity, suggesting that this may play a role in VOC.[55] Papadimitriou et al suggested that platelet inhibitors may have a role in prevention of VOC.[54] Levels of extracellular hemoglobin may also play a role in the development of VOC. Hemolysis resulting in release of excessive amounts of hemoglobin is a signature of SCD. Extracellular hemoglobin forms a complex with haptoglobin, but once the capacity of haptoglobin for hemoglobin is surpassed, excess extracellular hemoglobin can cause further complications.[55] Unbound extracellular hemoglobin in turn consumes the endogenous vasodilator nitric oxide, resulting in vasoconstriction and systemic and pulmonary

TABLE 1 Risk factors associated with VOCs and other SCD-related complications[25,28,50-63,79]

		References
Triggers	Patient factors: hypoxia, infection, fever, acidosis, dehydration, pregnancy, menstruation, obstructive sleep apnea, pain, anxiety, depression, alcohol consumption, physical exhaustion	50-52,62
	Environmental factors: exposure to temperature extremes, high wind speed, and humidity	50,51,53
	Comorbidities: sarcoidosis, diabetes, cholecystitis, herpes	51
Biomarkers	Blood parameters: high platelet and neutrophil counts, high hemoglobin levels, unbound extracellular hemoglobin, increased levels of plasma platelet factors 3 and 4, platelet hyperactivity	25,28,54-56
	Serum factors: high lactate dehydrogenase levels, elevated levels of fractalkine and fractalkine (*Fkn*) gene expression	57,60
	Inflammatory factors: reduced interleukin 10 (IL-10) secretion, levels of soluble CD163 > 1400 ng/mL, secretory phospholipase A2	57-59,61
Genetic predictors	Single nucleotide polymorphisms: +191 and +292 in galectin-3 gene (*LGALS3*), mutations in the γ-globin gene promoter that disrupt binding of major fetal globin repressors	63,79

Abbreviations: SCD, sickle cell disease; VOC, vaso-occlusive crisis.

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hypertension.[55] This hemoglobin also inhibits the cleavage of von Willebrand factor multimers, which then accumulate in the plasma and bind to platelets or sickled/fragmented erythrocytes to promote cell adhesion, leading to VOC.[55] A recent study in Nigeria found that higher hemoglobin levels, platelet and neutrophil counts, and avascular necrosis and leg ulcers were all significantly associated with a higher incidence of VOC.[56] A number of other metrics also have been shown to be predictive of the severity of VOC. For example, high levels of lactate dehydrogenase in serum have been associated with a severe evolution of VOC, especially in patients without ACS.[57]

A number of serum inflammatory markers potentially associated with VOC have been identified. However, increases in these markers are typically observed once a pain event has already begun, and therefore are connected to crisis severity rather than being predictive of onset. One report suggested that VOC occurs due to an imbalance in pro- and anti-inflammatory mechanisms associated with IL-10 signaling.[58] This study found that reduced IL-10 secretion was associated with an increased risk of VOC, possibly due to its effect on the pro-inflammatory cytokine TNFα. However, because of the design of the study, it is not possible to distinguish whether this was a consequence rather than a predictor of VOC. Another study suggested that levels of soluble CD163 > 1400 ng/mL were predictive of VOC and pulmonary hypertension.[59]

Elevated levels of serum fractalkine and *Fkn* gene expression in patients with SCD at steady state and during VOC indicate that it may be important in acute inflammation during crises. [60] In fact, it has been shown that serum fractalkine is elevated in patients with the highest frequency of VOCs and may be important in recurrent episodes. In addition, the potent inflammatory mediator secretory phospholipase A2 has been shown to be elevated in patients with VOCs who go on to develop ACS, and could be used to predict ACS development, and hence identify candidates for closer monitoring.[61] Moreover, asplenia, fever, reduced O_2 saturation, low Hb levels, and leukocytosis were also identified as predictors for the development of ACS.[62] Identification of imbalances in other inflammatory markers that predict severity and/or frequency of VOCs is needed in order to identify potential therapeutic targets and treatments.

4.β Genetic Predictors of VOC

While sickle cell anemia (SCA) is defined as the homozygous state for the HbS mutation, the SCD phenotype can be a result of several different genotypes.[63] Although hemolytic anemia and VOCs are found in varying degrees with all SCD variants, some genotypes are associated with more severe disease than others. This is in part due to varying cellular concentrations of HbS and therefore the degree of polymer formation.[63] Determining the specific genotypic variant present in an individual could help to predict the severity of disease. Also, specific genetic mutations have been associated with increased frequency of VOCs. For example, the presence of α-thalassemia is associated with increased risk of pain, and in a study to investigate the associations between single nucleotide polymorphisms (SNPs) of the GAL-3 gene (*LGALS3*) and serum GAL-3 levels with the frequency of VOCs in children with SCD, the presence of SNPs +191 and +192 in *LGALS3* resulted in intermediate serum GAL-3 levels, which may constitute a susceptibility factor for VOC frequency.[64] Other SNPs present in various genes have been associated with increased risk of stroke,[65] priapism,[66] and renal dysfunction.[67] The importance of determining the effect of genetic polymorphisms has been made a priority by the American Society of Hematology as a means of identifying patients at high risk of clinical events, including stroke, VOC, ACS, and progression of nephropathy.[68]

5 | MANAGING PAIN CRISES IN

The primary approach to the management of ongoing VOCs is pain control. Guidelines have been provided by the National Heart, Lung, and Blood Institute (NHLBI) regarding the management of acute and chronic pain in SCD, including pain associated with VOC.[46] The core elements of management of VOC include initiation of individualized opioid analgesia (ideally within 30 minutes), determining the most appropriate route of analgesic administration (oral, intranasal, subcutaneous, or intravenous), choosing an adequate starting dose (0.1 mg/kg morphine or 0.015 mg/kg hydromorphone), and repeating administration frequently as needed until pain improves.[31,46,50,69] If possible, an individual's prior history of pain control requirements during VOC should be used to determine appropriate dosing. In a recent phase 3 study, patient-specific dosing protocols, based in part on patient history, provided for better outcomes than a standard weight-based approach.[70] Patient-controlled analgesia can also be considered. However, results have been mixed, and certain studies have indicated that this is less effective than other forms of pain control, resulting in a longer length of stay by up to 8 days in patients aged 18-30 years and 13 days in those older than 30 years.[71]

Acetaminophen (paracetamol) and NSAIDs are widely used adjuvant therapies with opioids, not only because they can help to reduce the opioid requirement and reduce associated adverse events, but also because VOC is associated with increased inflammatory markers, including prostaglandin.[72] This is of interest because the anti-inflammatory and analgesic effects of NSAIDs are mediated via their inhibition of cyclooxygenase enzymes that convert arachidonic acid to prostaglandin.[73] In patients with VOCs associated with mild to moderate pain, NSAIDs can be used in place of opioids in patients who report pain relief with this class of drugs.[70] However, a randomized controlled trial indicated that the NSAID ketoprofen had no additional effect when given in combination with morphine.[74] Care must be taken with the use of NSAIDs in patients with SCD as some patients may have contraindications for their use. For example, acute renal failure may occur in subjects with chronic sickle nephropathy or other chronic kidney diseases when exposed to NSAIDs.[46] Other areas of concern include gastrointestinal, cardiovascular effects, and hypersensitivity caused by drug allergy or due to biochemical processes linked to arachidonic acid metabolism.[73,75] In addition, prostaglandins

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have a wide variety of effects, including induction of platelet aggregation, vasoconstriction and vasodilation, regulation of renal blood flow and glomerular filtration rate,[76] and regulation of circadian rhythms, reproduction, and homeostasis that could be affected by NSAID use in this population.[73] For patients with SCD with evidence of, or at risk of, end-organ damage, the use of NSAIDs may be contraindicated, especially in patients with rising serum creatinine.[46]

Potential adjuvant treatments include hydration, laxatives, antihistamines, antiemetics, intravenous fluids, and oxygen if the patient is hypoxic, and less commonly anxiolytics or non-pharmacologic approaches such as massage, acupuncture, yoga, and meditation.[31,45,50,77] Patients, especially children, who are experiencing emerging pain are advised to hydrate and take NSAIDs at home, provided there are no contraindications.

Recent studies have utilized mechanistic therapies to manage VOCs, but there are currently no approved drugs to treat patients who are experiencing VOCs. The investigational agent rivipansel is a synthetic pan-selectin inhibitor with effects predominantly mediated through E-selectin. Rivipansel was studied in a prospective, randomized, placebo-controlled phase 2 trial in patients experiencing VOCs. Although not statistically significant, the median time to resolution of VOC was 48% shorter than with placebo (69.6 hours vs 132.9 hours, respectively).[78] A phase 3 trial was completed, and rivipansel did not reduce length of stay or opioid use (ClinicalTrials.gov identifier: NCT02187003).[79] One possible explanation for the lack of efficacy was that the medication was given too late in the adhesion process. While the trial required administration of study drug within 24 hours of the first dose of IV opioid, some patients may attempt to manage pain events at home for several days. A preventative approach, with constant exposure of anti-adhesion agent, may be a more effective strategy to VOC prevention.

Higher levels of HbF are thought to be protective against VOC.[48,49] A recent study suggested that introduction of mutations into the γ-globin gene promoter disrupted binding of two major fetal globin repressors, BC11A and ZBTB7A. This may result in increased expression of HbF and thus help to prevent VOC.[80] Genome-editing technologies may therefore allow for new strategies in management of patients with SCD at risk of frequent VOCs.

6 | PREVENTIVE PHARMACOTHERAPY

Hydroxyurea is one of the most commonly used drugs for the management of painful crises in adult patients with SCD. It is indicated for reduction in the frequency of painful crises and to reduce the need for blood transfusions in adult patients with SCD with recurrent moderate to severe painful crises (generally at least three VOCs during the preceding 3 months).[46] In addition, NHLBI also recommends its use in patients who have pain that interferes with daily activities or quality of life, as well as in patients with a history of severe or recurrent ACS or severe chronic anemia that interferes with daily activities or quality of life, and to consider its use in infants > 9 months of age, children, and adolescents to reduce the incidence of SCD-related complications.[46] Hydroxyurea has been shown to increase levels of HbF, which appears to be protective against VOC.[81,82] In addition, hydroxyurea treatment has been associated with lower white blood cell, platelet and reticulocyte, and dense-cell counts; lower levels of adherent reticulocytes and leukocytes that may release pro-inflammatory cytokines may also help to prevent initiation of VOC.[81-83] Most importantly, hydroxyurea has been shown to reduce the number of pain episodes in adults with SCD, with an annual rate of VOC 44% lower than placebo ($P < .001$).[82] A 9-year follow-up study indicated that hydroxyurea also reduced mortality by 40%.[81] The optimal response to hydroxyurea occurs when the dose is titrated to a maximum tolerated dose that induces mild myelosuppression, with individual pharmacokinetics, pharmacodynamics, and pharmacogenomics contributing to the variability.[84] As a result, there may be limitations to its effectiveness, especially in clinical practice. While hydroxyurea is generally well-tolerated, some patients experience mild and reversible cytopenias leading to temporary suspension of treatment. A number of recognized and potential adverse events, many of which are rare, have been reported with hydroxyurea, including skin ulcers, pancytopenia, diarrhea, rash, vomiting, nausea, anorexia, and thrombocytopenia that may cause some patients to discontinue treatment.[84] Misconceptions about hydroxyurea-associated side effects and poor adherence are the greatest barriers to the use of and efficacy of hydroxyurea.[85]

Although less well established, a number of other possible treatments for management of patients with frequent VOCs have been approved or are in development. Studies have shown that supplementation with L-glutamine decreases endothelial cell adhesion, suggesting that it may be useful for prevention of VOC.[86] Although the mechanism of action is not well-understood, there is evidence suggesting that L-glutamine may improve the NAD redox potential of RBCs, thereby preventing oxidative damage to RBCs.[87] L-glutamine was approved by the US Food and Drug Administration (FDA) in 2017 to reduce the complications of SCD in adult and pediatric patients 5 years of age and older.[88] This approval was based on a clinical trial in 230 patients who had had at least two or more painful crises in the previous 12 months; all patients were stable on hydroxyurea for at least 3 months and continued treatment throughout the study. Over the course of the 48-week study, patients randomized to L-glutamine had fewer sickle cell crises (3 vs 4), fewer hospitalizations for sickle cell pain (2 vs 3), and fewer cumulative days in the hospital (6.5 days vs 11.0 days) than in those randomized to placebo, respectively. The median time to the first sickle cell crisis was 84 days for patients who received L-glutamine and 54 days for those who received placebo. There were also fewer occurrences of ACS in patients randomized to L-glutamine than placebo (8.6% vs 23.1%).[88]

Crizanlizumab has been approved by the FDA to reduce the frequency of VOCs in patients aged 16 years and older.[89] This humanized immunoglobulin G2 (IgG2) antibody inhibits P-selectin and blocks its interaction with its ligands, including P-selectin glycoprotein ligand 1 (PSGL-1), and interactions between endothelial cells, platelets, RBCs,

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and leukocytes,[89] thereby reducing VOC.[90] In a phase 2, multicenter, randomized, placebo-controlled trial in patients aged 16-65 years, crizanlizumab 5 mg/kg administered every 4 weeks (after a loading dose 2 weeks apart) with or without hydroxyurea was associated with a significantly lower annual rate of VOCs than placebo (1.6 vs 3.0, $P = .01$) and a significantly longer time to first crisis than placebo (4.1 vs 1.4 months, $P = .001$).[89] In a post hoc subgroup analysis of patients in the SUSTAIN trial who were VOC-free during the study, more patients were event-free in the crizanlizumab 5 mg/kg arm vs placebo, including patients with more frequent VOCs (ie, 5-10; 28.0% vs 4.2%), those who had the HbSS genotype (31.9% vs 17.0%), and those using hydroxyurea concomitantly (33.3% vs 17.5%).[91]

Voxelotor, formerly known as GBT440, is an allosteric modulator of hemoglobin-oxygen affinity that increases Hb affinity for oxygen, stabilizing RBCs in an oxygenated state and inhibiting HbS polymerization and the resultant sickling and destruction of RBCs. This results in improved blood rheology and hemodynamics. It was approved by the FDA in 2019 for the treatment of SCD in adults and pediatric patients 12 years or older.[92,93] Voxelotor received accelerated approval based on increases in hemoglobin levels, and this approval is contingent on the verification of clinical benefit in confirmatory trials. Phase 2 studies demonstrated improvements in hemoglobin levels and hemolysis.[94] Results from the phase 3 HOPE study of voxelotor in patients with SCD (N = 274) showed a significant increase in the proportion of patients with a hemoglobin increase > 1 g/dL (primary endpoint) with the 1500 mg dose (51%; $P < .001$) compared with placebo (7%) after 24 weeks of treatment.[95] However, there was only a trend toward a reduction in the annualized incidence rate of VOC between voxelotor and placebo in this study; additional research and follow-up are required to determine the effect of voxelotor on the frequency of VOC events.[95] In this study, voxelotor was generally safe and well-tolerated with a safety profile similar to that of placebo; there was also no substantial differences in the percentage of patients with SCD–related adverse events.[95]

Treatment of pain, especially chronic pain, with opioids does not address the underlying disease processes and may lead to hyperalgesia, dependence, and tolerance.[95] Indeed, opioids may adversely affect the membrane structure of RBCs, increase mast cell degranulation-induced inflammation, and activation of tyrosine kinases, all of which may contribute to VOC.[96] Prevention of pain associated with VOC is a preferred approach whenever possible. Avoidance of VOC triggers such as cold, fatigue, and stress can help to reduce the frequency of VOCs.[49,97] Another prevention strategy is avoidance of agents that may lead to initiation of VOC. For example, animal studies have suggested that vaso-constrictive agents such as α-adrenergic receptor agonists (including phenylephrine) may precipitate VOC.[98] Such agents should therefore be avoided in patients with SCD.

7 | CONCLUSIONS

Vaso-occlusive crisis in patients with SCD is a multifactorial process characterized by inflammation, adhesion, and multicellular aggregation of sickled RBCs, endothelial cells, platelets, and other blood cells, resulting in vaso-occlusion and acute severe pain. While management protocols to abort or ameliorate VOC by administration of opioids have been developed, the focus should shift to prevention of onset and reduction in frequency of pain crises, especially in those at higher risk. Research has identified a number of quantitative leads for identifying those patients at high risk of VOC. These patients may be good candidates for recently approved therapies in combination with hydroxyurea, such as L-glutamine and crizanlizumab, which take advantage of the underlying mechanisms of VOC and have been shown to reduce the frequency of this debilitating consequence of SCD.

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CONFLICT OF INTEREST

Dr Deepika S. Darbari is an advisory board member for Hilton Publishing Inc and a steering committee member for the Novartis SPARTAN study and has served on the advisory board for Global Blood Therapeutics. Dr Vivien A. Sheehan is an advisory board member for Pfizer and has received research grants from Novartis, Global Blood Therapeutics, and Emmaus. Dr Samir K. Ballas has served as a member of the speakers bureau for Novartis and has received honoraria from Novartis.

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